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Does the Type, Number or Combinations of Traditional Cardiovascular Risk Factors Affect Early Outcome After Carotid Endarterectomy?

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Purpose. *The present study was undertaken in order to assess the 30-day complication rate of carotid endarterectomy (CEA) in relation to the patients' cardiovascular risk factors.*
Methods. *Cardiovascular risk factors, operative details, morbidity and mortality of 1002 carotid endarterectomies in 852 patients were prospectively recorded in a database. The indications for surgery were asymptomatic ≥75% or symptomatic ≥50% internal carotid stenosis when other causes of stroke were excluded. Exclusion criteria were intervention for post-CEA restenosis, post-irradiation lesions, kinking of the internal carotid artery, external carotid artery stenosis, endovascular and simultaneous cardiac procedures.*
Results. *The 30-day combined minor and major stroke and death rate was 2.7% (27/1002). Significant risk factors in logistic regression model were diabetes (stroke and death rate=5.7%, p=0.002, OR=3.31), the simultaneous presence of three cardiovascular risk factors (stroke and death rate=5.3%, p=0.012, OR=3.11) and the combination diabetes, hypertension and hyperlipidemia (stroke and death rate=9.4%, p=0.001, OR=4.22).*
Conclusions. *Traditional cardiovascular risk factors significantly affect the 30-day stroke and death rate after carotid endarterectomy.*

Keywords: Carotid endarterectomy; Perioperative combined minor and major stroke death rate; Surgical risk; Traditional cardiovascular risk factors.

Introduction

Carotid endarterectomy (CEA) is a well-established method to prevent stroke in selected patients with symptomatic and asymptomatic high grade internal carotid artery stenosis.[1–3] The combined perioperative stroke and death rate should be ≤3% to achieve a beneficial effect of CEA over medical therapy.[4] Reports concerning the predictors of adverse outcome after CEA are often contradictory. A systematic review[5] of all studies published between 1980 and 1997 showed a higher operative risk of stroke and death in women, patients with symptomatic stenosis, age over 75 years, systolic hypertension, peripheral vascular disease, occlusion of the contralateral internal carotid artery and stenosis of the ipsilateral carotid siphon or external carotid artery. Data from the Ontario Carotid Endarterectomy Registry[6] demonstrated that a history of transient ischemic attack or stroke, atrial fibrillation, contralateral carotid occlusion, congestive heart failure and diabetes are significant independent predictors for 30-day death or stroke. Studies concerning the association between traditional cardiovascular risk factors and the incidence of overall stroke and death rates after CEA are limited. The aim of this study was to analyse if the type, the number or combinations of traditional cardiovascular risk factors affected the early outcome of CEA.

Materials and Methods

Between March 1988 and August 2005 we recorded prospectively the data from every patient who underwent carotid artery surgery. Interventions for post-CEA restenosis, post-irradiation lesions, kinking of the internal carotid, external carotid artery stenosis, endovascular and simultaneous cardiac procedures were excluded from this report.

A total of 1002 CEA interventions on 852 patients were included for this analysis. The indications for

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carotid surgery were asymptomatic ≥75% or symptomatic ≥50% stenosis of the internal carotid artery when other causes of stroke were excluded. The degree of stenosis was calculated based on angiography, according to the criteria of the European Carotid Surgery Trial (ECST).[7] We graded the comorbidities (cardiac, renal and pulmonary) and the cardiovascular risk factors using the scheme proposed by the Subcommittee on Reporting Standards for Lower Extremity Ischemia.[8] The clinical classification of carotid artery disease in our patients is reported according to the CHAT classification (Current status, History, Artery, Target).[9]

Before surgery all participants underwent a structural interview, clinical examination, ECG, chest X-ray and venous blood sampling collected after an overnight fast. Serum concentration of glucose, urea, creatinine, triglycerides, total and HDL-cholesterol were measured. LDL-cholesterol was calculated according to the Friedewald formula. History of smoking (none or abstinence >10 years; abstinence 1–10 years; current<one pack/day or abstinence<1 year; current≥one pack/day) was obtained. Diabetes was defined if the patient reported the use of antidiabetic medication. De novo diagnosis of diabetes mellitus was defined as the first demonstration of a fasting glucose serum concentration >126 or >200 mg/dl after oral glucose load. Hypertension was present if the diastolic pressure was >90 mmHg or if the subject reported current use of antihypertensive medication. Hyperlipidemia was defined as fasting serum concentration of cholesterol >190 mg/dl, LDL >115 md/dl or triglycerides >180 mg/dl.

Anaesthetic techniques, use of carotid shunting, clamping time, surgical techniques (conventional or eversion) and use of patch grafts were carefully recorded in the registry. All the patients were clinically evaluated by the surgeon (or in the case of stroke by the neurologist) on the first and the 30th post-operative day. Minor and major (permanent) strokes, deaths with its causes and all other perioperative surgical and medical complications were recorded. Clinical strokes were correlated with the results of brain CT scanning.

Statistical analysis was carried out using SPSS 12.0 for Windows program package (SPSS Inc., Chicago, IL, USA). The correlation between potential cardiovascular or surgical risk factors and 30-day overall minor and major stroke and death rate was assessed by univariate analysis using the Chi-square and Fisher exact tests. The variables that positively associated with post-operative outcome at $p<0.05$ were selected for multivariate analysis using forward stepwise logistic regression. Odds ratios (OR) and 95% confidence interval (CI) were calculated. A risk factor was considered statistically significant when $p<0.05$.

Results

Baseline characteristics and operative details are summarized in Table 1. Approximately two thirds of our patients were men, the mean age was 68.6 years (range 38–96 years), 61.1% were symptomatic (9.6% amaurosis fugax and 51.5% transient ischemic attack or stroke). Approximately 50% of the patients suffered from cardiac disease. 210 patients had ECG evidence of a previous myocardial infarction, 209 patients have stable angina, asymptomatic arrhythmia or drug-compensated congestive failure, and 66 patients had severe cardiac disease including unstable angina, symptomatic or poorly controlled arrythmia, poorly compensated failure or recent myocardial infarction (<6 months). Early in the experience we used

Table 1. Baseline characteristics of patients and surgical technique

	CEA	
	Number	%
Number	1002	
Sex		
Female	306	30.5
Male	696	69.5
Side		
Right	470	46.9
Left	532	53.1
Cardiac disease		
Yes	485	49
Not	517	51
Renal failure		
Yes	102	10.2
No	900	89.8
Pulmonary		
Yes	261	26.1
No	741	73.9
Clinical status		
Asymptomatic	390	38.9
Symptomatic	612	61.1
Stenosis		
Moderate (50–59%)	70	7
Severe/occlusion	932	93
Contralateral occlusion		
Yes	85	8.5
No	917	91.5
CEA technique		
Conventional	828	82.6
Eversion	174	17.4
Shunt		
Yes	548	54.7
No	454	45.3
Anaesthesia		
General	620	61.9
Regional	382	38.1
Median clamp time		
≤38 min	509	50.8
>38 min	493	49.2

Table 2. Traditional cardiovascular risk factors

	CEA	
	Number	%
Diabetes		
Adult no insulin	172	17.2
Adult insulin	86	8.6
Juvenile	7	0.7
Tobacco		
Abstinence 1–10 years	134	14.6
<1 pack/day	166	16.6
≥1 pack/day	225	22.5
Hypertension		
Single drug	424	42.3
Two drugs	267	26.6
Three drugs	74	7.4
Hyperlipidemia		
Mild diet controlled	231	23.1
Type II, III, IV	74	7.4
Drug controlled	275	27.4

Table 3. Combinations of traditional cardiovascular risk factors

	CEA	
	Number	%
One risk factor		
Dia	7	0.7
Tob	70	7
Hyp	92	9.2
Lip	39	3.9
Two risk factors		
Dia/Tob	15	1.5
Dia/Hyp	40	4
Dia/Lip	13	1.3
Tob/Hyp	118	11.8
Tob/llip	44	4.4
Hyp/Lip	147	14.7
Three risk factors		
Dia/Tob/Lip	6	0.6
Dia/Tob/Hyp	37	3.7
Dia/Hyp/Lip	96	9.6
Tob/Hyp/Lip	184	18.4

Dia, diabetes; Tob, tobacco; Hyp, hypertension; Lip, hyperlipidemia.

the conventional CEA technique with patch (Dacron® or vein) or primary closure under general anaesthesia and with routine intravascular shunting (with intraoperative electroencephalography monitoring). Later in the experience we introduced the eversion CEA technique under local anaesthesia with awake neurological testing. The median clamp time was 38 min. All the procedures were performed by or under supervision of the authors.

A review of the traditional cardiovascular risk factors (Table 2) showed that 76.3% of the patients were hypertensive, 57.9% had hyperlipidemia, 53.7% were smokers and 26.5% were diabetic.

Fig. 1 shows the presence of two or three cardiovascular risk factors in majority of the subjects.

Table 3 shows the combination of cardiovascular risk factors. 18.4% of the patients were current smokers and had hypertension and hyperlipidemia. Table 4 presents 30-day complications with an overall minor and major stroke and death rate of 2.7%. The cause of the 12 deaths was cardiac in four, stroke in three, suture ruptures in combination with severe hypertension in two, one combined stroke-cardiac, pulmonary, and venous patch rupture in one. Cardiac events were the most frequent non-lethal 30-day complication (2.6%) including symptomatic arrhythmia in 12 patient (1.2%), myocardial infarction in 10 patients (1%) and congestive heart failure in four patients (0.4%). Univariate analysis for 30-day stroke and death (Table 5) showed no significant influence of the described variables. Higher rates of adverse outcome were found in patients with occluded contralateral carotid artery (5.9 *versus* 2.4%, $p=0.058$) and in patients who underwent conventional CEA technique compared with the eversion technique (3.1 *versus* 0.6%, $p=0.057$); however the differences

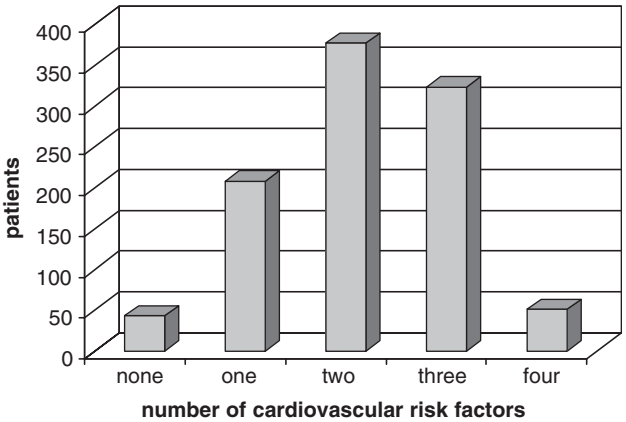

Fig. 1. Number of traditional cardiovascular risk factor per patient.

Table 4. Perioperative 30-day complications

	CEA	
	Number	%
Overall minor and major stroke and death rate	27	2.7
Permanent stroke	4	0.4
Transient stroke	9	0.9
Amaurosis fugax	2	0.2
Death	12	1.2
Cardiac	26	2.6
Pulmonary	16	1.6
Urinary	7	0.7
Digestive	7	0.7
Local neurologic	15	1.5
Infection	1	0.1
Haematoma/haemorrhage	27	2.7
Conservative treatment	12	1.2
Surgical treatment	15	1.5

Table 5. Risk factors for perioperative overall minor/major stroke and death (27/1002, 2.7%)

Variabe	Univariate analysis	
	p	OR (95% CI)
Bilateral CEA	0.502	0.73 (0.29–1.83)
Contralateral occlusion	0.058	2.54 (0.93–6.89)
Symptomatic stenosis	0.844	0.91 (0.41–2.21)
Severe stenosis	0.498	1.98 (0.26–14.8)
Women	0.844	0.92 (0.42–2.01)
≥75 years	0.867	0.92 (0.38–2.22)
Conventional CEA	0.057	0.17 (0.02–1.32)
Shunt	0.278	0.65 (0.30–1.41)
Patch	0.713	0.86 (0.39–1.90)
General/local anaesthesia	0.375	0.67 (0.29–1.56)
Clamp time>38 min	0.912	0.95 (0.44–2.05)
Comorbidities		
Cardiac	0.253	1.56 (0.72–3.41)
Renal	0.146	2.05 (0.76–5.55)
Pulmonary	0.382	1.43 (0.63–3.23)

OR, odds ratio; CI, confidence interval.

did not reach statistical significance. Rates of stroke alone (1/174, 0.6% *versus* 14/828, 1.7% $p=0.267$) and early carotid occlusion (2/174, 1.15% *versus* 16/828, 1.93% $p=0.743$) within 30 days of surgery were similar in the eversion and and conventional CEA group. Univariate and multivariate logistic regression models of cardiovascular risk factors predicting 30-day stroke and death rates are shown in Table 6. Strong independent predictors were diabetes (stroke/death rate=5.7%, $p=0.002$, OR=3.31), the presence of three cardiovascular risk factors per patient (stroke/death rate=5.3%, $p=0.012$, OR=3.11) and the combination diabetes, hypertension and hyperlipidemia (stroke/death rate=9.4%, $p=0.001$, OR=4.22).

Discussion

The combined perioperative minor and major stroke and death rate was 2.7% in our series, but the rate of permanent stroke and death was only 1.6%. NASCET,[10] ECST[11] and others[12] have reported comparable rates of adverse outcome. In contrast to the results of other investigators[5,6] we found no increased 30-day risk of stroke or death in women, nor in patients with symptomatic stenosis or aged over 75 years. Moreover a history of myocardial infarction, arrythmia or congestive heart failure did not influence the combined stroke and death rate. There was a trend ($p=0.058$) towards a higher perioperative risk of combined stroke and death in patients with contralateral occlusion. Further we noted a near significant lower rate ($p=0.057$) of stroke and death after eversion CEA (compared with conventional CEA), on the other hand rates of stroke alone and early carotid occlusion are similar in both techniques. It is difficult to definitively assess this early benefit of eversion technique because first this is not a randomised trial and second our findings may be biased by the fact that conventional CEA was performed during the earlier years.

To our knowledge we are the first to analyse the correlation between the type, the number and the combinations of traditional cardiovascular risk factors and the combined perioperative overall minor and major stroke and death rate. We found that diabetes was the only traditional cardiovascular risk factor identified as a strong predictor for stroke and death in

Table 6. Type, number and combinations of cardiovascular risk factor as independent factor for combined perioperative overall minor/major stroke and death (*N*=27/1002)

Variable	Univariate analysis		Multivariate analysis	
	p	OR (95% CI)	*p*	OR (95% CI)
Diabetes	0.001	3.62 (1.67–7.84)	0.002	3.31 (1.52–7.20)
Tobacco	0.654	0.84 (0.39–1.80)		
Hypertension	0.044	3.97 (0.93–16.88)	0.062	
Hyperlipidemia	0.034	2.60 (1.04–6.51)	0.076	
None risk factor	0.265			
One risk factors	0.273			
Two risk factors	0.203	0.57 (0.24–1.36)		
Three risk factors	0.001	3.71 (1.68–8.21)	0.012	3.11 (1.28–7.56)
Four risk factors	0.579	1.51 (0.34–6.56)		
Dia/Tob	0.516			
Dia/Hyp	0.938	0.92 (0.12–6.97)		
Dia/Lip	0.546			
Tob/Hyp	0.187	0.28 (0.03–2.09)		
Tob/Lip	0.438	1.77 (0.40–7.75)		
Hyp/Lip	0.596	0.72 (0.24–2.42)		
Dia/Tob/Lip	0.683			
Dia/Tob/Hyp	0.038	3.46 (0.99–12.05)	0.051	
Dia/Hyp/Lip	<0.001	5.10 (2.22–11.7)	0.001	4.22 (1.81–9.84)
Tob/Hyp/Lip	0.983	1.01 (0.37–2.70)		

OR, odds ratio; CI, confidence interval; Dia, diabetes; Tob, tobacco; Hyp, hypertension; Lip, hyperlipidemia.

the logistic regression model. Patients presenting three cardiovascular risk factors have a significant higher risk for perioperative complications then patients with none, one, two or four risk factors. Further statistical analysis of all possible combinations of cardiovascular risk factors demonstrated that patients presenting with diabetes, hypertension and hyperlipidemia have four times more risk for stroke or death than patients with other combinations.

Several reports[6,13] have demonstrated that diabetes is an adverse predictor for outcome, however, others[5,14] did not find differences in risk by diabetes. These conflicting results could arise from differences in population, number of patients, selecting criteria or methods. Another possible explanation for the contradictory reports concerning predictors is that in other studies each possible risk factor for adverse outcome is separately investigated and not the combinations. It is well known that pre-operative hypertension is the single most important determinant for the development of post-operative hypertension and the incidence of perioperative stroke and death rate is higher in patients with post-operative hypertension.[15] Skydell *et al.*[16] identified the factors that correlate with an increased incidence of post-CEA hypertension and found that 93% of these patients had diabetes mellitus. They postulated that diabetes may reduce the threshold for loss of central autoregulation leading to a positive feedback mechanism and resulting in increased blood pressure.

Our results demonstrate that diabetic patients with hypertension and hyperlipidemia are higher risk for adverse outcome following CEA. Carefully monitoring of blood pressure and aggressive treatment of peri- or post-operative hypertension is recommended in these patients.

Our study has several limitations. The study is a post-hoc analysis on a prospectively compiled database and during the study period different surgical techniques were used. Further we treated hypercholesterolemia and hypertriglyceridemia as one group of hyperlipidemia. However, several clinical studies have demonstrated that the presence of hypercholesterolemia correlates more closely with an increased risk of cardiovascular disease, than that of hypertriglyceridemia.

In conclusion, diabetes, the presence of three traditional cardiovascular risk factors per patient and the combination of diabetes, hypertension and hyperlipidemia have an adverse influence on the 30-day stroke and death rate of CEA.

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